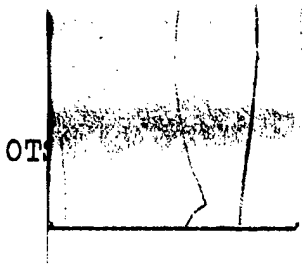

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THE ROLE OF ENDOCRINE GLANDS IN PROCESSES OF COMPENSATION OF FUNCTIONS OF THE ORGANISM

- USSR -

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THE ROLE OF ENDOCRINE GLANDS IN PROCESSES OF COMPENSATION OF FUNCTIONS OF THE ORGANISM[1]

/This is a translation of an article written by Ye. N. Speranskaya, Corresponding Member of the Academy of Medical Sciences USSR (Leningrad), in Problemy Endokrinologii i Gormonoterapii (Problems of Endocrinology and Hormonotherapy), Vol VI, No 1, Moscow, 1960, pages 3-9./

The basic vitally-important function of the organisms of animals and men is their reaction of adaptation to constantly changing effects of the external as well as the internal environment. The disorders of the ability to adapt to the changes of the surrounding influences lead to pathological states, i.e., to disease and loss of the adaptation reaction to death.

The leading physiological processes in the reactions of adaptation of the organism are adaptation and compensation of functions. The processes of adaptation and compensation are not well defined in their biological significance and complexity. This also follows from the exact translation of these words from Latin: adaptatio -- adaptation, accomodation; compensatio -- balancing, compensation. The first concept, as follows from the translation, does not require only special energy expenditure and is not fundamental, while the second concept indicates a prolonged process of rectification, which requires definite expenditures for compensation and, to balance out the interrelations of various physiological systems, a great effort of the entire organism is frequently required and then a large number of physiological mechanisms is included in the process of compensation.

In adaptation processes in the organisms of animals and man, the work of the organs apparently takes place within the physiological limits of normal viability, but it

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[1]Reported at the Session of the All-Union Institute of Experimental Endocrinology 26 March 1959.

proceeds on the level of either their low or their high activity. Thus, for adaptation processes, special, separate, more-or-less complex reorganization in the work of organs and systems of organs is not required. But the processes of compensation are connected precisely with manifestations of the reorganization of functions, frequently considerable, within separate physiological systems as well as in the interrelations of these systems with each other.

In the origination and course of the adaptation and compensation processes, the nervous system has a leading role; furthermore, with this a very essential role is played by the reorganization of the function of the endocrine glands as specialized organs whose function is directed to the realization and alleviation of nervous regulation. In the processes of the compensatory function of the organism, especially important significance is acquired by nervous trophicity as a factor which assures the reorganization of activity of tissues and organs not only in the functional but also in their structural respect.

In the present report I will dwell mainly on the processes of compensation and of the activity of endocrine glands in their realization. In the published literature there are sufficient references to the role of endocrine glands in processes of adaptation as well as to compensation of the functions of the organism.

We have previously pointed out [6, 7, 8] that in a study of the participation of the endocrine glands in processes which assure the compensatory function of the organism, these processes may be regarded in the light of three groups of manifestations which, however, in the whole organism basically take their course simultaneously.

First of all, these are the functional changes of activity of the endocrine glands in the development of compensation processes; second, structural reorganizations of the endocrine glands which take place in the development of compensatory manifestations and, third, functional changes of the work of separate organs or physiological systems which arise in connection with the changes of activity of the endocrine glands themselves. In the last case, in prolonged shifts of the work of the endocrine glands, morphological changes frequently may also appear (for example, hypertrophy of some body organs).

The compensatory manifestations in the activity of the endocrine glands begin not only in pathological conditions, such as, for example, in intoxications, traumas, septic diseases, etc., but they are also observed in a number of physiologically normal conditions which entail great stress on all functions of the organism, such as, for example, in

prognancy, in lactation, as well as in processes of acclimatization, etc.

The problems of compensation of functions of the organism is at present being studied by many researchers; however, still insufficient attention is being devoted to the role of the endocrine glands, whose hormones have great significance in the adaptation reactions ensured by the nervous system and its trophic function.

During the last few years, a number of data (2, 3) were obtained in the laboratory on compensation of the functions of the organism, in which we studied the significance of hormonal factors in the processes of reorganization of work induced by adaptation reaction.

One of the central organs that always participates in the basic functions of the organism in its various physiological as well as pathological conditions is the liver. The condition of the functioning ability of the liver also determines to a large extent the intensity of the compensatory possibilities of the organism.

Changes of functional condition of the liver were obtained by us by means of surgical intervention in which we disturbed its supply of the hormones of the pancreas, first of all insulin. The surgery consisted in transplantation of the ostium of the pancreaticoduodenal vein from the wall of the vena porta into the vena cava inferior. [6, 7, 8]. As a result of the surgery, the venous blood which flows from the upper part of the pancreas, and which is rich in insulin, bypasses the liver, directly reaching the general blood circulation. In small animals (mice, rat), and in rabbits as well as in dog, the changes of the liver's supply of insulin may be obtained by ligation of the pancreaticoduodenal vein; this operation produces analogous results. The decreased supply of insulin to the paronchyma of the liver and the system of vessels of the portal circulation induced definite shifts in its activity: its glycogenetic function decreased, its sugar-regulating and detoxicating functions changed, the activity of the cholinesterase of its tissue decreased, the bileforming processes were disturbed, etc.

All of the indicated changes had a functional character and leveled off 5-6 weeks after surgery. However, the full function of the liver was only apparent, since, in functional loading of the liver, which was accomplished by feeding the dogs meat exclusively for 2-5 days, all of the manifestations of insufficient function of the liver appeared anew and, being maintained for some time, again disappeared. They could be induced again by loading the liver (M.F. Bolovintseva and Ye. N. Speranskaya [3]; M.F. Bolovintseva [2].

As is known, the size of the liver in animals and in man under normal conditions of the organism may fluctuate considerably, which, however, does not depend on its filling with blood. The condition of prolonged physiological stress induces a considerable increase in it. Thus, for example, the liver of horses may double its weight in a prolonged process of acclimatization to the difficult high-altitude conditions of Tien-Shan [9].

The processes of work of the tissue of the liver and its regeneration are of great interest; therefore, in connection with the study of the compensation function of the organism, our co-worker I.A. Fashchevskaya conducted a special study of the regenerative ability of the liver under the conditions of an insufficient supply of insulin. In the published literature, there are references to the decrease of the regenerative function of the liver under changed hormonal influences. Thus, with removal of the hypophysis, Fransoen, Bruos and Richards [14] observed a decrease of liver regeneration in rats. This data was later confirmed by Canzanelli, Guild and Rapport [13] who discovered lagging in the regenerative ability of the liver of rats with removal of thyroid glands. From this point-of-view, the investigation of Milku, Boysler, Kostaner [4] is interesting; they showed that defficient function of the liver has significance in the development of hyperthyreosis.

In observations on rats I.A. Fashchevskaya discovered that under conditions of decreased supply of insulin to the liver, there is a regular decrease in the ability to regenerate liver tissue after surgical removal of a part of its lobes (about 60 percent of the weight of the organ). The difference of regeneration of the liver in the experimental group of animals with a ligated pancreaticoduodenal vein) as compared with the control group began to appear on the 14th day after partial removal of the liver and was expressed most sharply on the 48th day (Fig. 1).

The data obtained by application of X-ray irradiation to animals has especial interest. We have studied the development as well as the course of radiation sickness in animals with intact liver and in animals in which the liver function was decreased by surgery that induced the drawing off from the liver of a considerable amount of insulin, which is formed in the pancreas. With the influence of strongly injurious X-rays on an organism, a condition of great physiological stress is inevitably formed in the organism, under which the functions of compensation have a decisive significance. The animals in which the insulin supply of the liver was less than normal tolerated irradiation with X-rays with much more difficulty. The survival of

mice with an intact liver was considerably higher than that of mice in which the liver was partially deprived of insulin (Fig. 2). Dogs which withstood the surgical transfer of the osteum of the pancreaticoduodenal vein from the wall of the vena porta to the vena cava inferior also gave a sharp picture of radiation sickness and sometimes perished, while, in control animals, the development of radiation sickness and its course was considerably weaker. The sugar-regulating and detoxicating functions of the liver were more greatly disrupted than in the control animals (Fig. 3).

In the statement of materials we have limited ourselves to only one series of facts, namely to a discussion of the significance of the supply of insulin to the liver and the system of its portal vein for successful development of the processes of compensation; along the same lines, we also have data with respect to other hormones.

It should be stressed that great significance is held in the investigated scope of manifestations by the hormones of the adenohypophysis, the steroid hormones of the adrenal cortex, the hormones of the parathyroid gland and the hormones of the thyroid gland. The problem of the significance of corticosteroids for the functional condition of the liver and especially for its detoxicating function is most important. This is an important task for further study of the role of endocrine glands and of the significance of the liver in the processes of compensation of functions of the organism. No less important in the study of mechanisms which participate in the compensatory function of the organism is the problem of finding the conditions under which the manifestations of compensation may best be manifested. We possess some experimental data along this line.

As observations have demonstrated, one of the essential conditions of the successful development of compensation is the functional condition of the central nervous system, and the increased tonus of its higher regions has prime significance for optimum manifestation of compensatory reactions. The significance of the functional condition of the central nervous system in the processes of compensation of the organism is a problem which is not new. From ancient times it has been known to medicine that the basic guarantee of a patient's recovery, all other things being equal, is his faith in life, his desire to live, and that is precisely high tonus of the nervous system -- of its highest regions.

During the last few years, D.S. Tendler has been studying in the laboratory the development of manifestations of compensation of functions in dogs under excessive introduction of thyroid hormone. Prolonged intoxication of dogs

with large doses of thyroidine was performed for the duration of 3 - 8 months in doses of 0.3 to 1 g per kg of body weight. For clarification of the optimum conditions for the development of compensatory functions in the organism of animals, thyroidine was given in various series of experiments in various ways. Some dogs received 1 g of thyroidine per kg of body weight daily; to others 3 g of thyroidine per kg. of weight was given every 3rd day; thus, the animals received during the same period of time identical amount of thyroidine, but with days inbetween that were free of introduction of the preparation.

The degree of thyroidine intoxication we judged according to the changes of a number of physiological indexes in animals. In all experimental dogs the consumption of O_2 under the conditions of determining the basal metabolism according to Goldan, body weight, pulse, number of respiratory movements, functional condition of thyroid gland according to the absorption of radioactive iodine (I^{131}) and its introduction were studied; in all animals the conditioned-reflex activity was studied.

It is interesting that feeding of the same large quantities of thyroidine over a prolonged period of time but by different methods, i.e. daily or every third day, produces a different effect according to the intensity of intoxication which was present in the animals. The intoxication was considerably more sharply expressed with daily introduction of thyroid preparation 1 g per kg of weight than with introduction of 3 g per kg of weight every 3rd day. This could be judged according to a number of indexes, among them the weight of the dog (Fig. 4). Also noted was a sharp difference in the amount of increase of oxygen consumption under the conditions of various methods of feeding with thyroidine, the increase of oxygen consumption under the conditions of basal metabolism on the 17th week was on the average 47% of the initial level, while, in feeding with thyroidine once every 3rd day, during the same period the increase of oxygen consumption under the conditions of basal metabolism was on the average only 22% of the initial level. During the course of the following 5 months of dog thyroidinization, the increase of the metabolism level remained within the same limits; furthermore, during this period days were frequently observed when the consumption of oxygen was normal; in dogs with daily introduction of thyroidine the normal values of oxygen consumption under the conditions of basal metabolism appeared only during the 8th month of introduction of the preparation. Thus, the manifestations of compensation develop worse with daily introduction of thyroidine.

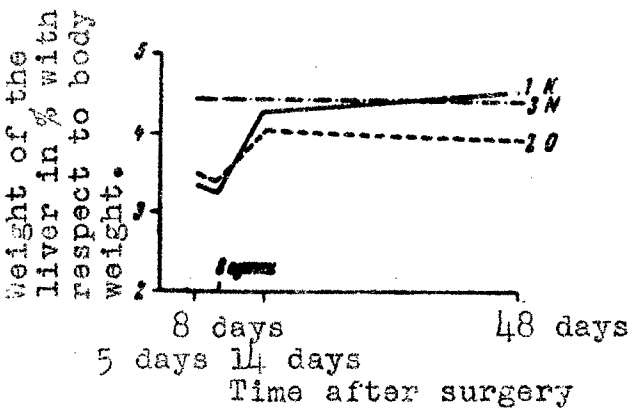

Fig. 1. Relation of weight of the liver to body weight of rats in percent (average arithmetical data).

Intact 40 rats (3); control 40 rats with partial removal of liver lobes (1); experimental 40 rats with partial removal of liver lobes and simultaneously ligated pancreaticoduodenal vein (2).

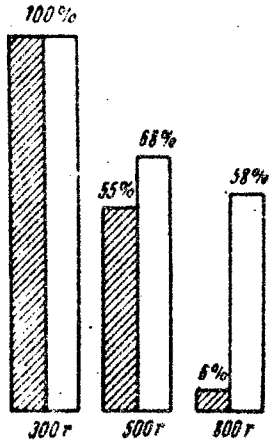

Fig. 2. Percent of mice surviving after irradiation with X-rays: 300 r, 500 r, and 800 r.

Crosshatched columns - mice operated (ligation of pancreaticoduodenal vein) 6 days before irradiation (206 mice). White columns - mice, operated at the same time, but the vein was not ligated - control (105 mice).

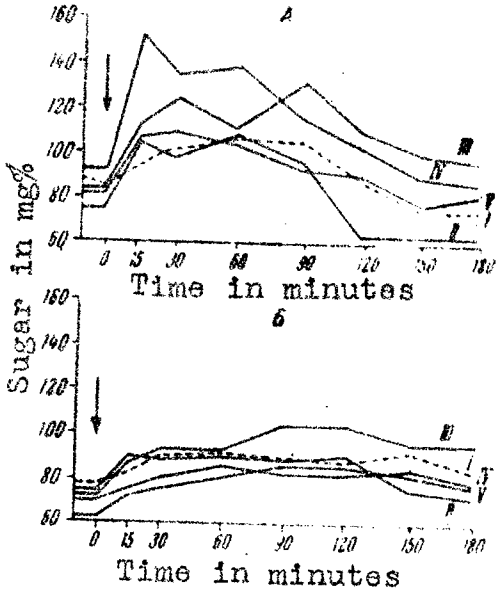

Fig. 3. The curves of blood sugar level of 2 dogs in alimentary loading with sacharose (.) (to I) and after irradiation with X-rays (two times 300 r each) at different times (curves on: II-13th day; III-21st day, IV-60th day; V-after 6 months).

A- dog was operated 2 months before irradiation (transplantation of the osteum of the pancreaticoduodenal vein from the wall of the vena porta into the wall of the vena cava inferior), by the time of irradiation had a normal course of glycemic curves under loading per os with sacharose; B- control dog.

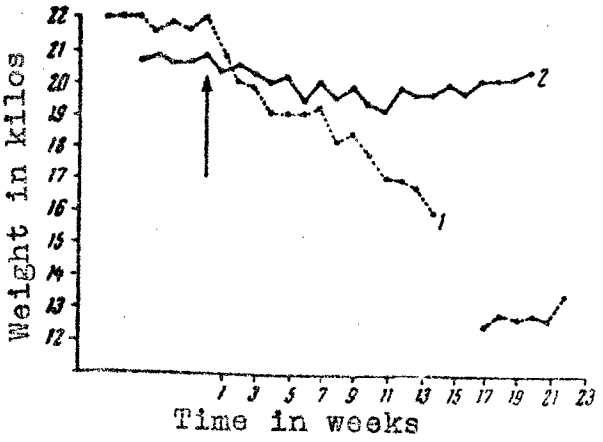

Fig. 4. The curves of body weight of dogs. The beginning of feeding of thyroidine is denoted by an arrow.

1- weight with introduction of thyroidine daily in a dose of 1 g. per kg of body weight; 2- weight with introduction of thyroidine every third day in a dose of 3 g. per kg of body weight.

Disturbances of higher nervous activity of dogs were clearly expressed under both methods of feeding thyroidine.

Under both methods of introduction of thyroidine, the curves of absorption of radioactive iodine by the thyroid gland and its excretion on the second day showed the absence of the formation of thyroid hormone by the thyroid gland of the dog. Under conditions of intensively supplying the organism with thyroid hormone, the termination of formation of thyroid hormones by the dog's own thyroid gland is one of the first mechanisms of compensatory function of the organism in its struggle against excessive quantities of this hormone.

The above-mentioned experiments on dogs showed that the compensatory manifestations develop in the organism more successfully with fractional introduction of thyroidine than with daily introduction. Abelin [12,11] also observed greater resistance in rats with introduction of large doses of thyroidine with free days inbetween than with daily intoxication.

Apparently, the development of compensatory processes takes a better course when there are days without the introduction of thyroid hormone, during which the organism apparently continues to intensively mobilize its compensatory potentialities.

The presence of such a mechanism was also indicated by I.P. Pavlov in his pronouncements on clinical "media" [5]. This moment, it appears to us, should have special practical interest with respect to endocrine diseases under hormone therapy and specifically in substitution hormone therapy. The introduction of the appropriate hormone quickly normalizes metabolic processes, rectifies the function of an endocrine gland, and provides a possibility for the development in it of compensatory processes with respect to its functional changes as well as morphological reorganization. This, for example, may take place in the correct insulin therapy of diabetes.

In a study of conditions which may assist the development of the manifestations of compensation, we made an attempt to clarify the role of the tonus condition of the nervous system in the manifestation of compensatory reactions, and, first of all, in the mobilization of mechanisms which would assure the normal activity of higher regions of the nervous system.

Among the first indexes of thyroid intoxication, as we have already reported [1], are the changes of canine conditioned-reflex activity. This is also observed with introduction of insignificant doses of thyroidine (0.002 g per kg of weight), which do not induce changes of O_2

consumption under conditions of basal metabolism. In subsequent investigations, D.S. Tedler studied the changes of higher nervous activity with introduction of large doses of thyroidine. The dog received 1 g of thyroidine per kg. of body weight every 3rd day. This dose was sufficiently large, which was indicated by the termination of the formation of thyroid hormone by the thyroid gland of the dog, as was established by the absorption of I^{131} by the gland.

During the control period the stereotyped conditioned alimentary reflexes were produced in the dog; they were studied daily under two different method conditions. First of all, in a chamber of the half-open type, with placement of the dogs on the stand and registration of saliva secretion and second, under the conditions of free behaviour, when the dog moved freely during the experiment, from one side of the room where she was on a mat, to the other side of the room for receiving food under positive conditioned stimuli. Under these experimental conditions the moments at which the dog ran to the feeder, of its arrival at the feeder where food was thrown to it, and of its return to the mat where it lay during the experiment, were automatically registered on a kymogram. The conditions of this method allowed one to register the latent period of conditioned reflexes, the time of the running of the dog and its reaction to a differentiated stimulus. The time interval between the experiments, according to conditioned reflexes under the conditions of free behavious and the experiment in the changer, was 5 hours; both experiments were performed daily. After the control period, which lasted more than 3 months, the dog started to receive 1 g. of thyroidine per kg. of weight every 3 days.

It was possible to judge the processes of compensation according to the above-mentioned indexes: comsumption of O_2, body weight, etc.

In this dog, right after the beginning of feeding thyroidine, there was a clear difference in the nature of conditioned reflexes during the same day under different methodical conditions of conducting the experiment. Under conditions of limiting the movements of the dog in placing it on the mat immediately after the beginning of thyroidinization, considerable disturbances of higher nervous activity began; these were expressed in a decrease of positive salivary reflexes, release of the differentiation with manifestations of an ultraparadoxal phase, refusal of food, motor unrest, barking during stimuli and in the intervals between them, etc. Under conditions of a free-movement method of conducting the experiments, the disturbance of higher nervous activity was not observed: the dog, functioned

clearly the same as before introduction of thyroidine; only after 1½ months after the beginning of thyroidinization was a disturbance of differentiation noted and the second time this was observed was after a month, after which for longer than a month the conditioned-reflex activity was faultless.

The cited data evidence the significance of the tonus of the cerebral cortex for the development of the process of compensation, which, as was shown by P.S. Kupalov and his co-workers, is increased under conditions of free behavior of the animal during the experiment.

The significance of the functional condition of the nervous system for the development of compensatory manifestations was also observed by us in the neoplasm of the Langerhans island apparatus of the pancreas in adult rats with an intensive administration of carbohydrates into them. Ye. V. Stroganova [9] observed that in neurotic conditions of the animals, the neoplasm of insulaes is absent in glucose loadings, while in normal animals this compensatory reaction of the organism, in response to glucose loading, always appeared quite distinctly.

Thus the development of compensatory processes in the organism and the involvement of various physiological mechanisms which assure the functional and structural reorganizations of the endocrine glands as well as of a number of physiological systems of the organism or individual organs have a great dependence upon the functional condition of the central nervous system.

The study of the processes of compensation of the functions of the organism not only has great theoretical significance but is also important for practical medicine.

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